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EXAMINER	
GRASER, JENNIFER E	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/773,792	DUBENSKY ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-41 and 61-88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-41 and 61-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/31/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted on 7/31/07 is made. Claims 22-41 were previously examined. New claims 61-88 have been added.

It is noted that the species election directly applies to all new claims, 61-88, e.g., species: a mutation in *actA* and *inlB*. Accordingly, not all of the recited species in the new claims are under examination.

Claim Objections

1. Applicant is advised that should claims 61-68 be found allowable, claims 69-75 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

The claims 61-68 and 69-75 are identical. It is suggested that Applicants delete claims 69-75.

Claim Rejections - 35 USC § 112-2nd paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 22-41 and 61-88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is vague and indefinite because it attempts to claim the bacterium by function alone. It is unclear what *structure* is encompassed by 'attenuation both for entry into non-phagocytic cells and for cell-to-cell spread'. The metes and bounds of the claim cannot be understood. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. The claim should provide any structural properties which would allow for one to identify the bacterium without ambiguity. See also enablement and written description rejections. Applicants arguments have been fully and carefully considered but they are not deemed persuasive in overcoming the rejection. The structure of the claim is entirely vague and indefinite. The broadly recited functions do not allow for one to ascertain the structure of the bacterium being claimed for patent protection. The claims fail to correlate in scope to the gene mutants which Applicants have described in the instant specification. There is no specific structural alteration recited in claim 22.

Claim 23 recites the limitation ""the mutation" in line 3. There is insufficient antecedent basis for this limitation in the claim. There is no 'mutation' recited in the claim from which it depends.

Claim 25 remains rejected as vague and indefinite because it is unclear whether the reaction causing the modification is the same 'reaction, mutation, etc.' which cause the attenuation in claim 22. The metes and bounds of this claim cannot be understood.

Claim 27 is vague and indefinite because it is unclear what is encompassed by the phrase 'defective with respect to one or more internalins'. How are they defective? What is encompassed by this language? The amendment of the claims 'respective to wild-type' does not overcome this rejection. Does the term 'defective' mean the internalin has been rendered completely inactive, partially inactive, etc.?

Claim 30 is vague and indefinite because it is unclear what is encompassed by the phrase "defective with respect to ActA". Does this mean the ActA gene has been deleted, etc.? The metes and bounds of this language cannot be understood. How is the ActA defective? The amendment of the claims 'respective to wild-type' does not overcome this rejection. Does the term 'defective' mean the internalin has been rendered completely inactive, partially inactive, etc.?

Claim 39 recites the limitation "the antigen" in the last line of the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 22 does not recite 'an antigen'. It appears that this claim should be dependent on claim 33 which recites 'the antigen' and not claim 22 which does not require an antigen. Clarification and/or correction is requested.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 22-38 and 83-88 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-122 of copending Application No. 10/883,599. Although the conflicting claims are not identical, they are not patentably distinct from each other because the co-pending claims encompass any bacterium which has been attenuated for proliferation by reaction with a nucleic acid targeted compound that reacts with the nucleic acid (see instant claims 25 and 26). The phenotypes 'attenuated for entry into non-phagocytic cells and for cell-to-cell spread' are forms of proliferation and are, therefore, encompassed in the language of the claims from 10/883,599. Co-pending claims 13 and 16 recite that the microbe is a bacterium, more specifically L.moncytogenes and co-pending claim 18 encompasses mutations in both the actA and inlB genes. Co-pending claims 113 and 120 recite the same tumor antigens as the heterologous antigens recited in instant claim 35. Both applications teach the use of these bacterium as vaccines. Accordingly, since the

scope of the instant claims is encompassed by the Genus recited in 10/883,599 the scope of the claims are not patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 39, 40 and 61-82 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20-149 of copending Application No. 10/773,618. Although the conflicting claims are not identical, they are not patentably distinct from each other because the co-pending claims encompass methods which use any bacterium which has been attenuated for proliferation by reaction with a nucleic acid targeted compound that reacts with the nucleic acid (see instant claims 25 and 26). The phenotypes 'attenuated for entry into non-phagocytic cells and for cell-to-cell spread' are forms of proliferation and are, therefore, encompassed in the language of the claims from 10/883,599. Co-pending claims 13 and 16 recite that the microbe is a bacterium, more specifically L.moncytogenes and co-pending claim 18 encompasses mutations in both the actA and inlB genes. Co-pending claims 113 and 120 recite the same tumor antigens as the heterologous antigens recited in instant claim 35. Both applications teach the use of these bacterium in methods inducing an immune response to antigen and methods for treating or preventing a disease in a host. Accordingly, since the scope of the instant claims is encompassed by the Genus recited in 10/773,618 the scope of the claims are not patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112-Enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 22-41 and 61-88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are broadly drawn to an isolated *Listeria* bacterium which is attenuated both for entry into non-phagocytic cells and for cell-to-cell spread (the elected Group mutations in both actA and inlB). The instant specification has taught a double mutant (mutations in both actA and inlB) which has been deposited with the ATCC as accession number PTA-5562. The instant specification has demonstrated that this mutant strain was eliminated very quickly in the liver as compared to other strains tested, even though it was given in the highest dose. The mutant was shown to elicit an immune response in mice. However, the specification has not taught (through challenge experiments) that this bacterium may provide protection (vaccine) or prevent infections caused by Listeria. Treatement of Listeria *monocytogenes* infection has been enabled, but not prevention or protection. The specification has not shown that

this deposited bacterium, or any other prophetic bacterium, can treat or prevent cancer (as newly claimed). The standard for cancer treatment is extremely high and it is unpredicatable.

The claims are broadly drawn to obtaining attenuated Listeria bacteria by mutating variant nucleotide sequences from many different species of Listeria yet the specification has only taught mutation of the actA and inlB genes from *L.monoctyogenes.* In the present case, the applicant has neither provided any direction or guidance, nor any working examples in the specification as to any potential mutations of actA and inlB genes from other species of Listeria that would satisfy the limitations of the claims. The claims read on any mutation to the L.monocytogenes inlB and actA genes, and to homologs thereof, that have the effect of decreasing the activity of the gene product. Just as the breadth of the claims is great, so is the number of potential mutations that may be made. Not only are there numerous substitutions that may be made, but there are also large numbers of insertions and deletions that may be made in the polynucleotide sequence. Although the number of operative embodiments is also likely to be high, the lack of guidance leading to them tends to show that they are not readily identifiable. Thus, the factors of claim breadth, guidance, and quantity of experimentation tend to favor a finding of undue experimentation.

While those participating in the art of the relevant technology (genetic and protein manipulation) are generally highly skilled, the art is also rife with complexity. See also, discussion above in the written description rejection (demonstrating the lack of obviousness as to what mutations may be operable absent guidance). Knowledge of the

sequence of protein or polynucleotide alone is not sufficient for those skilled in the art to make any mutation to a molecule and have confidence as to the effects that such a mutation would have. See e.g., Bowie, supra. Although Bowie also points out that information gathered from groups of similar or related proteins often helps in making predictions as to the effects of particular mutations. Bowie, pages 1308-1309. However, while the applicant has provided a few related proteins in the specification, there is no discussion as to the structural relationships among them. Rather, the sequences are set out, and it is left to those in the art to run comparisons to determine what the similarities among them are, and to determine which of them are important and which are not. In short, that applicant has invited others in the art to determine what mutations would achieve the desired affect without providing them any guidance indicating what the potential operable embodiments are.

The instant claims encompass mutations in control sequences, the coding sequence or in a gene that controls expression of inlB or actA. It is disclosed that the function of the mutated gene may be from 25-100% less than the protein produced from a non-mutated gene sequence. See page 28. The specification fails to teach which portions of the actA and inlB gene are necessary for entry into non-phagocytic cells or for cell-to-cell spread. Accordingly, the scope of the instant claims is not enabled.

The use of these numerous different bacterium to treat or prevent ***any*** infectious disease, e.g., parasitic, fungal, bacterial from any Genus/species, viral, etc., and or to treat or prevent cancer is ***highly*** unpredictable. There are no results or working examples, which are required in such highly unpredictable arts, that enable the scope of

these method claims. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

Given the complexity of the art, the breadth of the claims, the number of potential mutations, and the lack of guidance provided by the applicant, the examiner finds that there is insufficient information in the specification to enable those skilled in the art to practice the claimed invention without undue experimentation. The specification does not provide evidence that one skilled in the art would know what modifications, and what regions of inlB and actA to target for modifications, in order to produce an attenuated bacterium with the desired phenotype. Applicant's demonstration in the instant Specification that a species of mutant cells may serve as an effective vaccine does not enable one skilled in the art to make mutations in any Listeria bacterium, in such a way as to not only attenuate the bacterium through the specific mutation of the inlB and actA, but to also decrease the biological activity in such a way that it is responsible for the resultant attenuated bacterial phenotype. Genentech Inc. v. Novo Nordisk A/S

(CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. Bowie et al was also cited for providing evidence that information gathered from groups of similar or related proteins may not be sufficient to show one skilled in the art where to make mutations in a molecule and to have confidence that the mutations will have the desired result (Bowie, pages 1308-1309). Given the complexity of the art, the breadth of the claims, the number of potential mutations, and the lack of guidance provided by the applicant, the examiner finds that there is insufficient information in the specification to enable those skilled in the art to practice the claimed invention without undue experimentation.

Response to Applicants' arguments:

Applicants argue that their working examples demonstrate that ability of an *actAinlB* **double *deletion*** mutant strain of ***Listeria monocytogenes*** to induce an immune response against an antigen, treat tumors in an in vivo **mouse** model (not protection against cancer (any and all types) was not shown) is specifically taught in the

specification. This has been fully and carefully considered. Applicants' arguments are not commensurate in scope with the claimed invention which is drawn to any isolated Listeria bacterium with attenuation for both entry into non-phagocytic cell and for cell-to-cell spread with no recited description of a particular mutation. The dependent claims encompass an ***extremely*** broad scope of possible mutations to an extremely large number of different genes. The specification does not enable this scope of invention, which also includes treatment and protection methods against any infection disease, e.g., parasitic, viral, fungal, bacterial, etc., and any type of cancer in humans or other mammals. Applicants arguments address a specific bacterium, an *actAinlB* **double *deletion*** mutant strain of ***Listeria monocytogenes***, but the claims are not drawn to this bacterium or its use in the claimed methods. Accordingly, the rejection stands.

Claim Rejections - 35 USC § 112-Written Description

9. Claims 22-41 and 61-88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to any Listeria bacterium which is attenuated for entry into non-phagocytic cells and for cell-to-cell spread and is not limited to an *actAinlB* **double *deletion*** mutant strain of ***Listeria monocytogenes*** such as recited in the instant Examples. The claims are drawn to an attenuated Listeria bacterium which is obtained mutating *any* actA and inlB gene from *any* bacterium of the Listeria Genus

(elected Group). The claims also are drawn to vaccines comprising these attenuated bacterium. These claims read on mutations of the inlB and actA genes, or attenuated bacteria comprising such polynucleotides, and species homologs thereof. However, the specification does not provide adequate written description to support either species homologs to L.monocytogenes actA and inlB genes, or any mutation resulting in attenuation for entry into non-phagocytic cells and cell-to-cell spread.

There is inadequate written description to support claims to species homologs.

The claims are broadly drawn to obtaining attenuated Listeria bacteria by mutating genes from many different species of Listeria, yet the specification has only disclose mutations in the inlB and actA genes of *Listeria monocytogenes.*

The applicant has not identified any common structural core which one skilled in the art could use to identify any genus of polynucleotides to be mutated. In essence, the applicant is claiming such mutants comprising homologues only by their functionality, that of attenuated cell-to-cell spread and entry into non-phagocytic cells. More than a statement of biological function is required to satisfy the 112 1st paragraph written description requirement for a genus of DNA molecules. See e.g. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 U.S.P.Q.2d 1016, 1027 (CAFC 1991); and Fiers v. Revel, 25 U.S.P.Q.2d 1601, 1604-05 (CAFC 1993). In Amgen v. Chugai, the Court of Appeals for the Federal Circuit stated that "[i]t is not sufficient to define [a DNA] solely by its principal biological property, e.g. encoding of human erythropoietin." Id., at 1021. Rather, "what is necessary is that [the applicant] provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of

his claims." Id., at 1027. In these statements, the court has expressly stated that a DNA molecule must be described by means of description other than by naming the encoded protein to satisfy the 112 ¶1 written description requirement.

More recently, the Federal Circuit again took this position. In the case University of California v. Eli Lilly and Co., 43 U.S.P.Q.2d 1398, at 1406 (1997), the court stated that defining a cDNA by its function "is only a definition of a useful result rather than a definition of what achieves that result." The court also stated that such a description "does not define any structural features commonly possessed by members of the genus [of claimed cDNAs] that distinguish them from others." Id. Thus, it is clear that identification of mutant bacterium by naming the phenotype of the gene it encodes is not sufficient. In the present case, the only description that the applicant has provided for species homologues of inlB and actA is that they must also be responsible for cell-to-cell spread and entry into non-phagocytic cells. Such a description is clearly insufficient to support the claimed genus. The specification does not provide evidence that one skilled in the art would know what modifications, and what regions of the inlB and actA coding regions to target for modifications, in order to produce an attenuated bacterium. While it may be obvious to those in the art to make mutations in a gene or protein, to achieve an attenuated bacterium, once the molecule has been identified as necessary for the virulence of the bacterium, it is not immediately obvious to those in the art as to what mutations will be effective. See e.g., Bowie et al., Science 247:1306-1310, page 1306. Bowie et al. presents a discussion on the tolerance of proteins to substitutions in the residue sequence. Although the reference is a discussion of protein substitutions, as

the present case is concerned with polynucleotides encoding such proteins, the teachings of the reference are equally applicable to the mutations of the claimed inventions. The reference states first that proteins generally accept a wide variety of substitutions in their residue sequence. However, it also states that some residues may not be substituted at all without loss of the proteins function. The reference also states that the effects of such substitutions are, currently, highly unpredictable. Thus, one skilled in the art would not be able to recognize from the current disclosure any substitutions, or other mutation (except, perhaps, deletion of the whole polynucleotide) that would result in a decreased gene product activity.

As stated above, the Federal Circuit has held that claiming polynucleotides disclosed by their biological function alone is inadequate to meet the written description and enablement requirements. In the present case, not only does the application claim additional undisclosed polynucleotides without such support, it further claims modifications to both the disclosed and undisclosed polynucleotides by the effect of such modifications.

Applicants are claiming bacteria and they are claiming said bacteria comprising a mutation in a nucleotide sequence with a specific structure: function relationship in the claims. "The Applicant's are not claiming polynucleotide sequences per se."

It is the position of the examiner that the novelty of the instantly claimed invention not only lies in the coding sequence of the inlB and actA polynucleotide sequences recited in the claims, but the polynucleotide sequence must additionally be mutated in such a way as to decrease the biological activity (cell-to-cell spread and entry into non-

phagocytic cells) in order to attenuate the bacteria. The polynucleotide sequence, as well as the specific mutation(s) of the polynucleotide sequence to accomplish decreased biological activity of the encoded polypeptide, is critical to the invention, e.g, not just the phenotype displayed by the mutant bacterium.

The Specification does not provide any examples or provide any detailed description of the inlB and actA gene such that one skilled in the art would be aware of, or recognize that Applicant was in possession of, any such mutated bacterium. Applicant has not provided any guidance as to which parts of the gene are susceptible to mutation such that they would result in the expression of an inactive or less active protein thereby resulting in decreased virulence and attenuation of the bacterium. There is no description of any of the gene mutations, or any targets for mutation, that could yield the intended results. Thus, the applicant has not provided any working examples of or any guidance towards, the claimed mutations. The applicant is therefore claiming a genus of mutated bacteria solely by their intended effects, without providing any structural or other information by which one skilled in the art could identify the claimed inventions.

The application need not describe every possible change to the coding sequence for a polypeptide that would result in meeting the claims' functional limitations. However, such does not absolve the Applicant of the need to provide some structural description by which those in the art could distinguish mutated genes resulting in the attenuated bacterium. Applicant must describe a representative number of species for a claimed genus, but what is now claimed, is a highly variable genus (mutant poly-nucleotides)

which result in variable levels of biological activity, and expression (see all claims), for which deposited mutant strain is not representative.

Response to Applicants' Arguments:

Applicants argue that actA and inlB genes had been identified in a representative number of Listeria species at the time of filing and that some methods of attenuating cell-to-cell spread or entry into non-phagocytic cells that are taught in Applicants specification are independent of the knowledge of the actual sequences of specific genes whose expression products are involved in cell-to-cell spread or entry into non-phagocytic cells. These arguments have been fully and carefully considered but are not deemed persuasive. The instant claims are drawn to any isolated Listeria bacterium which is attenuated for entry into non-phagocytic cells and for cell-to-cell spread with no recited structural features and is not limited to an *actAinlB* **double *deletion*** mutant strain of ***Listeria monocytogenes*** such as recited in the instant Examples. The specification fails to provide examples of these other bacterium and the claims are not limited to actA and inlB deletions from any species. Applicants' arguments are not commensurate in scope with the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The bacterium and the mutation to the nucleic acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 22-24, 27-30, 32, 37, 38, and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Appelberg et al (Infect. Immun. Feb. 2000. 68(2): 912-914).

Appelberg et al teach mutants of *Listeria monocytogenes* which are defective in cell invasion *and* cell-to-cell spread. They teach an isolated *Listeria monocytogenes* mutants which are defective in the ***actA*** gene, the *plcB* gene and the *inlA* and ***inlB*** genes. These mutant strains were shown to be less virulent than wild-type strains. See abstract. These mutants were injected into mice and the immune response was monitored. The term "vaccine" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A "physiologically acceptable carrier" reads on water and therefore would be inherent in the preparation of the mutants. The reference specifically recites that "it will be interesting to analyze the characteristics of double mutants defective in both the ActA and the internalin pathways". See paragraph bridging pages 913-914.

Response to Applicants' Arguments:

Claims 22-24, 27-30, 32, 37, 38, and 39 do not require double mutations as argued by Applicants. The only pending claim, claim 31, which recited a mutation in

both actA and inlB was not included in the rejection. Claims 22-24, 27-30, 32, 37, 38, and 39 use the language 'at least **one** mutation in **one** *or* more genes. Claim 22 does not even require a specific mutation in any gene, but may read on a naturally isolated attenuated strain. None of the claims are limited to a *actAinlB* **double *deletion*** mutant strain of ***Listeria monocytogenes*** such is the focus of the arguments. Appelberg et al specifically teaches mutants of *Listeria monocytogenes* which are defective in cell invasion *and* cell-to-cell spread (see title) and do not require the cells to be double mutants much like the claims which are rejected. There may be other pathways than the act and inl genes for these functions. The mutants taught by Appelberg possess the same functional limitations as instant claim 22 and the identical structural limitations of claims 23-24, 27-30, 32, 37, 38, and 39, e.g., 'at least **one** mutation in **one** *or* more genes'. The reference teaches that the ability of different strains to invade heatocyctes could be from a mutation in the lecithinase gene or in the internalins. See pg. 913, column 2. Applicants arguments are not commensurate in scope with the claimed invention.

14. Claims 22-24, 27-30, 32, 37, 38 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Drevets (Infect.Immun. Jan. 1998. 66(1): 232-238).

Drevets teaches mutants of *Listeria monocytogenes* which are defective in cell invasion *and* cell-to-cell spread. Drevets teaches isolated *Listeria monocytogenes* mutants with deletions of the ***actA***, *inlA*, ***inlB***, *inlAB*, *plcA* and *plcB*. These mutant strains were shown to be less virulent than wild-type strains. See abstract. These mutants were injected into mice and the immune response was monitored. The term

"vaccine" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A "physiologically acceptable carrier" reads on water and therefore would be inherent in the preparation of the mutants.

Response to Applicants' Arguments:

Applicants argue that Drevets do not specifically recite a single bacterium that is attenuated for both entry into non-phagocytic cells and cell-to-cell spread. They argue that just the showing that the mutant strains taught by Drevets to be "less virulent than wild-type strains" is insufficient to indicate that these strains are attenuated for both entry into non-phagocytic cells and cell-to-cell spread. These arguments have been fully and carefully considered, but are not deemed persuasive. Drevets teaches isolated *Listeria monocytogenes* mutants with deletions of the ***actA***, *inlA*, ***inlB***, *inlAB*, *plcA* and *plcB*. Accordingly, these claims contain the structural limitations for attenuation for both entry into non-phagocytic cells and cell-to-cell spread. The phrase "are attenuated for both entry into non-phagocytic cells and cell-to-cell spread" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. The mutants with delections of both the *actA* and *inlB* genes would inherently possess this functionality.

Further, it is noted that several of the non-elected species are also taught by Drevets. A discovery of an inherent property of a known product does not impart novelty.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Appelberg et al (Infect. Immun. Feb. 2000. 68(2): 912-914), as applied to claims 22-24, 27-30, 32, 37, 38, 39 above.

The teachings of Appelberg et al are set forth above. The reference teaches mutants of *Listeria monocytogenes* which are defective in cell invasion *and* cell-to-cell spread. They teach an isolated *Listeria monocytogenes* mutant which is defective in the ***actA*** gene, the *plcB* gene and the *inlA* and ***inlB*** genes. These mutant strains were shown to be less virulent than wild-type strains. See abstract. Although the reference does not specifically teach a mutant with mutations in both the ActA and internalin pathways, it would have been prima facie obvious to one of ordinary skill in the art to generate such a mutant because Appelberg et al specifically recite that "it will be interesting to analyze the characteristics of double mutants defective in both the ActA and the internalin pathways" because they hypothesize that invasion of hepatocytes by an ActA mutant is mediated by the InlAB-induced internalization of the bacteria directly by the hepatocytes". It is disclosed that this is critical to the way in which the bacterium

can cause severe infection. See paragraph bridging pages 913-914. Accordingly, one of ordinary skill in the art would have been motivated to produce a mutant deficient in both ActA and inlB in order to find a way of treating such a virulent infection.

Response to Applicants' Arguments:

Applicants argue that for a 103 rejection, a reference must teach or suggest each every claim limitation. This is not the proper standard for a 103 rejection. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Further, the following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) **A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains**. Patentability shall not be negatived by the manner in which the invention was made.

Applicants focus on the fact that the double mutant defective in both ActA and the internalin pathways was not made at the time of publication of the reference. This is irrelevant. What is relevant is the motivation provided in the reference for the production of this double mutant. A 103 reference does not have to teach with certainty what a future product would produce or then it would be a 35 USC 102 reference and not a 103 rejection. Given the fact that the prior art at the time the invention was made

teaches the function for both the interalin pathway and ActA gene, it would have been *prima facie* obvious for one of ordinary skill in the art to create such a double mutant since doing so would create a less infective/pathogenic microorganism. The exact motivation for producing an identical structure does not have to be the same as Applicant's motivation for producing the structure. Appelberg et al specifically recite that "it will be interesting to analyze the characteristics of double mutants defective in both the ActA and the internalin pathways" because they hypothesize that invasion of hepatocytes by an ActA mutant is mediated by the InlAB-induced internalization of the bacteria directly by the hepatocytes". It is disclosed that this is critical to the way in which the bacterium can cause severe infection. See paragraph bridging pages 913-914. Accordingly, one of ordinary skill in the art would have been motivated to produce a mutant deficient in both ActA and inlB in order to find a way of treating such a virulent infection.

17. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571)

272-0858. The examiner can normally be reached on Monday-Thursday from 7:30 AM-6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

Jennifer Graser 10/5/07
Primary Examiner
Art Unit 1645